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CASE SERIES

Physicians' Experiences as Patients with Statin Side Effects: A Case Series

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Abstract Physicians are among those prescribed statins and therefore, subject to potential statin adverse effects (AEs). There is little information on the impact of statin AEs on physicians affected by them. We sought to assess the character and impact of statin AEs occurring in physicians and retired physicians, and to ascertain whether/how personal experience of AEs moderated physicians' attitude toward statin use. Seven active or retired physicians from the United States communicated with the Statin Effects Study group regarding their personal experience of statin AEs. AE characteristics, experience with (their own) physicians, and impact of AE was ascertained. We inquired whether or how their experience altered their own attitude toward statins or statin AEs. Patient A: Atorvastatin 40 then 80 mg was followed by cognitive problems, neuropathy, and glucose intolerance in a Radiologist in his 50s (Naranjo criteria: probable causality). Patient B: Atorvastatin 10 mg was followed in 2 months by muscle weakness and myalgia in an Internist in his 40s (probable causality). Patient C: Atorvastatin, ezetimibe/simvastatin, rosuvastatin at varying doses was followed shortly after by irritability, myalgia, and fatigue in a Cardiac Surgeon in his 40s (probable causality). Patient D: Simvastatin 20 then 40 mg was followed in 4 years by mitochondriopathy, myopathy, neuropathy, and exercise intolerance in an Emergency Medicine physician in his 50s (definite causality). Patient E: Simvastatin 20 mg and niacin 1000 mg was followed in one month by muscle weakness and myalgia in a Physical Medicine and Rehabilitation physician in his 50s (probable causality). Patient F: Lovastatin 20 mg then simvastatin 20 mg, atorvastatin 20 mg, rosuvastatin 5 mg, niacin 20 mg and ezetimbe 10 mg was followed by muscle weakness and myalgia in an Obstetrician/Gynecologist in his 70s (definite causality). Patient G: Ezetimibe/simvastatin and atorvastatin (dose unavailable) was followed shortly after by cognitive problems in a Radiologist in her 80s (probable causality). Thus AEs affected multiple quality-of-life relevant domains, often in combination, encompassing muscle ($N = 5$), fatigue ($N = 2$), peripheral neuropathy ($N = 2$), cognitive ($N = 2$), dysglycemia ($N = 1$) and behavioral manifestations ($N = 1$). In five, the AEs affected the physician professionally. Five physicians experienced dismissive attitudes in some of their own healthcare encounters. One noted that his experience helped not only his own attention to statin AEs, but that of other physicians in his community. Several stated that their experience altered their understanding of and/or attitude toward statin AEs, and/or their view of settings in which statin use is warranted. Statin AEs can have profound impact in high functioning professionals with implications to the individual, their professional life, and those whom they serve professionally.

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Key Points

This is the first analysis to address the experience of physicians themselves affected by adverse effects (AEs) of statin medications, encompassing muscle, neuropathic, cognitive, and behavioral AEs.

The impact of statin AEs in physicians can be profound, professionally and personally, in some cases requiring major professional modification or early retirement.

Poor awareness of statin problems by medical providers, and low receptiveness to reports of such problems, can extend even to patients when they themselves are physicians.

Introduction

Statins (HMG-CoA reductase inhibitors) are among the best-selling prescription drugs and have been viewed as having a favorable safety profile, but like all drugs, they bear potential side effects. While adverse effects (AEs) are reported to be rare in clinical trials, they are less uncommon in clinical experience [1, 2]. It has been observed that physicians often dismiss the possibility of statin-related etiology when patients present with side effects linked to statin use [3], and that patients with statin AEs commonly perceive that their physicians do not appreciate the quality-of-life impact of their AE [4].

Physicians, current and retired, are among those who take statins. There are two reasons for our interest in statin AEs in physicians. First, consideration of AE impact has focused primarily on direct health ramifications and has not investigated professional consequences to the individual. Properly contextualizing the impact of statin AEs requires attention to this additional dimension. Second, patients with statin AEs have communicated instances in which their physician became more receptive to the possibility of statin AEs when the physicians themselves or their personal family or professional contacts developed statin AEs. We were interested in the issue of whether experiencing a statin AE altered physicians' own attitudes regarding statin AEs reported by others.

We present seven cases of statin AEs in physicians.

Method

The Statin Effects Study is a patient-targeted statin AE reporting effort approved by the University of California, San Diego Human Research Protections Program (HRPP). Materials were reviewed to identify individuals who had communicated with the study group and noted that they were physicians. Fourteen physicians who had reported statin AEs were identified. Ten qualifying individuals provided informed consent and completed a self- or interviewer-administered HRPP-approved survey, which elicited information on subject characteristics including risk factors for statin AEs [5], statin usage, adverse effect features, professional impact, adherence to Naranjo criteria, and the subject's experience within the medical community. Using the Naranjo Adverse Drug Reaction (ADR) probability scale, cases were coded as meeting criteria for doubtful, possible, probable or definite presumptive statin AE causality. Three cases lacked a trial off statins, followed by improvement, limiting the causality determination to at most "possible"; these cases were therefore excluded, providing seven cases that are presented.

For brevity, two cases are highlighted in the text, with five additional cases detailed in a table. For purposes of exposition, cases have been assigned arbitrary, alphabetically-ordered, letter labels (unconnected to subject names).

Results

Dr. A, a radiologist in his 50s, stated that he developed marked cognitive problems and also neuropathy shortly after increasing his atorvastatin dose from 40 to 80 mg/day. Effects were new, marked, sustained, and interfered with his work, leading to difficulty understanding case presentations, to radiology reading errors (including right/left errors on readings), and to placement of orders for the wrong patients. These consequences to his professional accuracy led him to fear medicolegal repercussions. He did not share his cognitive concerns with his own physician, leery of risks and ramifications from such disclosure. However, he did share the neuropathy symptoms. His physician, whom Dr. A noted bore a "Top Doctor" designation, stated that no further assessment was warranted for neuropathy symptoms except in diabetics. No suggestion was made by his doctor of a possible statin role, or suggestion for a trial of statin discontinuation, until a medical student commented on the association of neuropathy to statin use. Discontinuation of statins, after 3 years of sustained symptoms, led to rapid and striking improvement in cognitive function. By a week after discontinuation, Dr. A noted dramatic cognitive recovery, which he perceived to be approximately complete. He observed more gradual recovery of neuropathy symptoms, which he characterized as having improved by an estimated 95% at 8 months (improvement having apparently plateaued at that level).

Dr. B is an internist in his 40s who reported that, 6 weeks after commencing statins, he developed rapidly progressing muscle symptoms comprising fatigue, pain, weakness and shortness of breath. Numerous specialist referrals occurred and tests were conducted, and concerns regarding possible amyotrophic lateral sclerosis (ALS) were expressed. Ultimately a muscle biopsy showed mitochondrial myopathy that was attributed in the biopsy pathology report to statin use (compatible literature is available [5–7]). Statin discontinuation was undertaken after only ~2 months of statin use, and although what had been a rapid progression of symptoms fully arrested, according to the patient, recovery was limited and remains partial, 13 years later. Professional impact of his statin-related problems was marked: he discontinued inpatient care, call, and curtailed his hours, patient volume, and pay, also refitting his offices with higher desks and chairs to enable him to slide off chairs to rise.

Medical specialty, age at symptom onset, sex, statin, dose, risk factors, adverse effect, and Naranjo Causality score for these two and five additional physician cases are presented in Table 1. Information on the five additional affected physicians, with further cognitive, muscle, neuropathic, and adding behavioral AEs, are provided in Table 2 with brief details on the AEs, interaction with physician, referrals/tests/diagnoses, effect on attitude as a physician, as well as professional impact (where relevant).

These cases illustrate key points. AEs of statins include muscle [4], cognitive [8], neuropathy [9], and behavioral symptoms [10] (among others) and physicians and retired

Table 1 Synopsis of physician cases

Case	Medical specialty	Age at symptom onset	Sex	Statin	Dose (mg)	Risk factors	Adverse effect	Naranjo causality
Dr. A	Radiology	50s	M	Atorvastatin	40,80	High dose[a]	Cognitive Neuropathy Glucose intolerance	6 Probable
Dr. B	Internal medicine	40s	M	Atorvastatin	10	[c]	Muscle weakness Myalgia	5 Probable
Dr. C	Cardiac surgery	40s	M	Atorvastatin	20, 40	High dose[a]; combination with other lipid lowering agent	Irritability Myalgia	7 Probable
				Ezetimibe/ Simvastatin	10/40		Fatigue	
				Rosuvastatin	20, 40			
Dr. D	Emergency Medicine	50s (start statins) 60s (max symptoms)	M	Simvastatin	20, 40	Familial risk, high dose[a]	Mitochondriopathy Myopathy Neuropathy Exercise intolerance	9 Definite
Dr. E	Physical medicine and rehab	50s	M	Simvastatin Niacin	20 1500	Active athlete; combination with other lipid lowering agent	Muscle weakness Myalgia	5 Probable
Dr. F	OB/Gyn	70s	M	Lovastatin	20	Diabetes	Muscle weakness Myalgia	9 Definite
				Simvastatin	20			
				Atorvastatin	20			
				Rosuvastatin	5			
				Niacin	20			
				Ezetimibe	10			
Dr. G	Radiology	80s	F	Ezetimibe/ simvastatin Atorvastatin	[c] [c]	Age, female, PAD[b]	Cognitive	7 Probable

M male, *F* female, *OB/Gyn* obstetrics and gynecology, *PAD* peripheral arterial disease

[a] High dose defined as the potency equivalent of simvastatin 40 mg or higher

[b] Linked to oxidative stress, mitochondrial dysfunction, and all Metabolic Syndrome factors, which in turn are risk factors

[c] Not known

Table 2 Further information on the five additional cases

Dr. C Irritability Muscle pain Fatigue	(1) Following initiation of statins, Dr. C developed fatigue and muscle pain. New development of irritability/short temper toward coworkers, though not noted by Dr. C., was noted by coworkers, leading to professional action/referral. Statin discontinuation led to resolution of fatigue/muscle symptoms (judged by Dr. C) and irritability (judged by coworkers)
	(2) At Dr. C's suggestion of a possible statin link, Dr. C's physician acknowledged that he had heard of side effects with rosuvastatin at the 40 mg dose. At Dr. C's request, the psychiatrist to whom his employer referred Dr. C communicated with physician investigators familiar with behavioral changes as a manifestation of statin AEs, who advised that the behavioral manifestations could represent a statin AE, with likelihood of a statin foundation augmented by concurrent development of fatigue and muscle symptoms. On this basis the statin was discontinued
	(3) Dr. C's employer referred him for psychiatric evaluation because of behavioral problems at work
	(4) Dr. C. previously held statins in favorable opinion, he now says, "I have no interest in going back on statins." He reports awareness that statins can lead to behavioral changes, and deems more education on statin AEs is needed
	(5) Professional review, psychiatric evaluation
Dr. D Mitochondriopathy Myopathy Fatigue Exercise intolerance	(1) Dr. D. experienced a clear decline in exercise tolerance that progressed over a 4 year period on statins, with development and progression of myalgias ultimately rated 8–9/10 in severity, and extreme lethargy. Discontinuation of statins led to gradual improvement in muscle pain: 3.5 years after statin discontinuation, he reports 75% improvement in myalgias, however, there has been no discernible improvement in exercise intolerance
	(2) Dr. D's non-physician sister proposed the statin connection after she herself suffered intolerance. Dr. D's physicians were generally dismissive of a statin connection. Dr. D describes a "pervasive skepticism" at the idea, with physicians "rolling their eyes" at the suggestion, even when he presented them with literature supporting the relationship
	(3) Referrals were made to cardiology, rheumatology, and neurology. Testing encompassed blood tests, MRI brain and spine, multiple cardiac catheterizations, EMG/NCS, and ultimately a muscle biopsy with mitochondrial testing. The NCS identified conduction problems of unclear etiology. The biopsy report read "reproducible abnormalities were found most prominently in complexes II-III (succinate cytochrome C reductase) and complex IV (cytochrome C oxidase) with reductions to 12 and 18% of their respective normal means. This patient is considered to have statin-induced myopathy"
	(4) Dr. D. described his own prior attitude toward statins as "elementary and naïve, that they were bad in some people, but that there would be clear manifestations and happen quickly within weeks. I thought a normal CK would essentially rule it out, that the symptoms were largely reversible." He now emphasizes that the side effects "can be very disabling, can happen in substantially delayed fashion, the CK can be normal"
	(5) Disability from statin AEs contributed to retirement
Dr. E Muscle weakness Muscle pain	(1) Dr. E tolerated simvastatin for 13 years, however after a 2 year trial off, he resumed simvastatin with niacin. He retired early to pursue athletic adventures, but a month after recommencing statin and niacin, developed new exercise intolerance, rapid muscle fatigue, and loss of muscle strength. He discontinued the statin a month later. Two years later, although notable improvement has occurred, there remains a significant residuum
	(2) Dr. E's experience with the healthcare system was unfavorable. He felt his doctors were unsympathetic, and that his symptoms "did not register much concern" from them
	(3) Neurological evaluation with NCS/EMG showed atypical proximal muscle unit abnormalities, slowed nerve conduction, and fasciculations. Brain and spinal MRI were negative. He also saw a urologist for low testosterone (simvastatin has been shown to reduce testosterone [27, 28]), but a 4 month trial of testosterone replacement did not confer benefit
	(4) Dr. E's perspective following this experience is that "statins should not be prescribed to those who are athletically inclined." He observes that they have "a very real propensity to adversely impact the mitochondria on a permanent basis"
	(5) N/A, already retired
Dr. F Muscle weakness Muscle pain	(1) Dr. F developed muscle pain and weakness (to the point where he could no longer drive) with each of a succession of lipid lowering medications (most statins), with improvement when these were discontinued. However, an extensive cardiac history caused trials off statins to be short-lived. For instance, atorvastatin was stopped in 2000 when his weakness became severe, and improvement in walking was noted 2 months later, but rosuvastatin was prescribed due to elevated cholesterol levels, resulting in a rapid return of weakness
	(2) Dr. F's interaction with the medical system was relatively positive. Although his cardiologist initially dismissed the possible connection of statins to his weakness, when the cardiologist's own family member developed similar statin AEs, he began to investigate the relationship
	(3) Dr. F. was referred to neurology and endocrinology, had blood tests, NCS/EMG, and muscle biopsy. He received successive diagnoses of arthritis, diabetic neuropathy, depression, and normal aging. His muscle biopsy showed changes consistent with mitochondrial myopathy on histology (based on ragged red fibers and Cox staining), without confirmatory evidence on electron microscopy
	(4) Prior to his own experience, Dr. F. had no strong opinions about statins. He felt they were mostly safe and certainly indicated for people with cardiovascular disease. Now, whenever he and his wife (also a physician) notice gait abnormalities in their friends and even strangers, they inquire whether or not they are on statins
	(5) N/A, already in the process of retiring

Table 2 continued

Dr. G Cognitive problems	(1) Shortly after statin initiation, Dr. G developed confusion, disorientation, and short-term memory loss. She asked repetitive questions and had a short attention span. Statins were discontinued, followed by marked improvement in cognitive function. A month after discontinuation, she recalled running into one of her former colleagues in the grocery store and being able to immediately recognize the person (a clear improvement over her prior state). This acquaintance exclaimed that she looked much better than 8 months previously, when they had last interacted (2) Dr. G's physician dismissed the potential statin connection. Her son stated, "He replied in a condescending tone of disbelief that I 'read too much'" (3) Dr. G. was referred to a neurologist, and treated with donepezil for a year under the assumption the cognitive problems may be Alzheimer's. Other diagnoses that had been considered included depression and pseudo-dementia (4) Not known (5) Disability from statin AEs contributed to retirement

(1) Statin AE synopsis; (2): Interaction with Physician; (3): Referrals/Tests/Diagnoses; (4): Effect on Attitude as a Physician; (5): Professional Impact

AE adverse effect, *CK* creatine kinase, *EMG* electromyography, *NCS* nerve conduction study, *MRI* magnetic resonance imaging

physicians are not exempt from risk. AE cases reported here have evidence for at least probable statin causality [11]. Career implications of statin problems can arise from cognitive and muscle problems, as in the two cases above, as well as from behavioral AEs of statins (Case C in Table 2). Each have potential for impact to physicians' career, and some AEs, perhaps particularly cognitive and behavioral AEs, have potential for ramifications to patients. (We did not elicit, and participants did not volunteer, instances—if any—in which such ramifications were realized.) Physicians seen by individuals affected by statin AEs (including physicians seen by physicians reporting such AEs) were commonly unfamiliar with these statin AEs, and for five of the cases, some of the physicians consulted were initially dismissive [3].

Many participants experienced professional impact. In neither cases of Dr. A nor Dr. B did the physicians caring for the statin-affected physician-patients have an understanding of the potential causal role of statins initially. Dr. A was informed of the possible connection of statins to neuropathy not by his physician, but by a medical student working with his physician, who was aware of the reported association. Dr. B's statin experience occasioned the positive development of increased awareness of statin adverse effects—and vigilance for them—both in himself (though still affected, he has retained a primary care practice) and among other physicians in his community. Finally, both physicians saw arrest of progression, and symptom improvement after discontinuing the statin, however neither returned fully to their previous health states [7, 12]. (Dr. A states that he retains some residual neuropathy, though it has markedly abated.) We emphasize that for each of the reported symptoms, recovery profiles (in time course and completeness) vary across affected individuals; the swift reported recovery of cognitive function reported by Dr. A is on the rapid end of the recovery-time course spectrum.

Discussion

To our knowledge, this is the first report to address statin AEs in physicians and to evaluate how experiencing a statin AE affected physicians professionally, how knowledgeable and receptive these physicians find other professionals to be in professional encounters, and whether and how experiencing statin-associated problems influenced their own (and if known, other physicians') attitudes towards statin AEs. These cases underscore that commonly reported statin AEs—here encompassing muscle [4], cognitive [8], fatigue [13], neuropathic [9], and behavioral [10]—also afflict high functioning professionals such as physicians, in whom these symptoms can have profound professional implications, contributing in some to early retirement (Table 2) or persistent disability. These cases reprise a number of observations from other settings. Symptom onset can be delayed [4, 8]. Older age is a risk factor for statin AEs [5, 14, 15], and people continue to age while taking statins—moreover, physiological aging may be accelerated by the processes that underlie statin AEs [5]. Higher dose increases risk (Drs. A, C, D) [5]. For those who remain on statins after the first symptom arises, emergence of symptoms spanning several categories is not uncommon, likely reflecting common pathophysiological foundations [5]. Rarely, symptoms may initially worsen with discontinuation. (We note this is consistent with evidence that antioxidant effects can arise (and reverse) quickly, prior to lipid effects [16]; while some prooxidant effects, linked for instance to recovery of lipid transport of antioxidants, may take longer to reverse. This may, in some, engender an initial worsening of *statin-induced* prooxidant-antioxidant balance, on statin discontinuation.) Resolution of AEs can be incomplete (whether by patient report or objective testing) [6, 7] and residual disability may be profound [4, 17]. Statin AEs, including muscle wasting, weakness, and exercise intolerance as well as

neuropathy perhaps in particular [18] (but also cognitive dysfunction) may fail to fully resolve clinically [19, 20] and pathologically [7]. (Indeed, there may be failure of full resolution pathologically even when there is apparent clinical resolution [19].) Persistent muscle problems can reflect mitochondrial myopathy [5–7]. Regarding cases in Table 2: Behavioral symptoms may be recognized by others rather than the individual in whom they occur (Dr. C) [21, 22]. Athletes may be at special risk for statin muscle problems (Dr. E) [23, 24]. Physicians seeing those who experience statin AEs may be dismissive of symptoms or of a possible statin connection—even, we find here, when reported by physicians-as-patients [3].

In addition to reprising previous findings regarding the symptoms themselves, these cases offer new insights into impact. Professional impact in these cases varied depending on the nature and severity of the AEs—and the proximity to planned retirement—from no professional effect to early retirement to significant curtailment of hours and income, professional review, and fears about patient consequences and medicolegal action. Costs for evaluations and referrals may be high. Some physicians, on whom patients (including other physicians) rely for compassion and care, may fail to take statin-related problems seriously and may fail to follow-up on possible statin associations of symptoms, while other physicians are receptive, and responsive, to experiences and concerns of their patients. Patients may not reveal cognitive symptoms to their physicians fearing repercussions of disclosure. This may lead to delays in addressing the cause, which can increase prospects for repercussions to the patients whom the physician serves. Physicians reported that their experience altered their attitudes toward statins, reflecting awareness of potential for symptoms, but also increased appreciation of the impact such symptoms can have. Each of the AEs described here has been documented in the literature in association with statins; discussion of potential mechanisms of these statin AEs can be viewed in other sources [5–7].

As in other case series and AE surveillance approaches, there is no defined base population or control group, so relative rates and risk-ratios cannot be calculated. However, rates and risk-ratios are not the goal. Since the purpose is to characterize and understand these AEs and their potential impact, only subjects who have experienced an AE are relevant. Like all studies with volunteer subjects, there is self-selection, which may affect generalizability; however AE reports are in any case about illustrating potential effects, not normative ones. Subjects with mild symptoms may not feel motivated to share their experiences; those with extremely severe symptoms may be unable to do so. Regarding the most severe problems, there is the additional limitation that statin AEs can seldom qualify as meeting presumptive criteria for probable or definite AE causality if there was no improvement after drug discontinuation. Thus, people who continue on statins with symptoms or those in whom a progressive or irreversible problem may have been triggered are excluded from consideration. Self-reported data may be influenced by recall and reporting bias, but this shortcoming affects all questionnaire studies. Most importantly, even if the findings reported here apply only to a subset, they remain important for that subset. Prior studies have shown that patient AE self-reporting can be a reliable, valuable tool [25, 26]. Additionally, Naranjo presumptive causality criteria provide an independent form of causality estimate, and the seven cases presented met literature-based criteria for definite or probable AE causality. Physicians' experience of statin AEs is among a suite of factors that could influence approaches to statin prescribing; whether or how these experiences influenced prescribing, in practitioners who prescribed statins, was not assessed.

Conclusion

This case series, with its focus on physicians, underscores the quality-of-life and professional impact that can attend statin AEs, and reinforces the understanding that consequences can be persistent. Greater awareness of these problems, and greater compassion when patients present with these conditions may be merited. Lessons drawn from these physicians-as-patients have relevance to other professions. (For instance, delay in addressing the cause of cognitive compromise may have repercussions for those served by the professional, not only for doctors but for pilots, drivers, lawyers, nuclear facility workers, drug/chemical/vehicle production personnel, and many other professionals.) Care should be taken in management decisions in relation to statin use to limit unnecessary occurrence of AEs, and to recognize and mitigate the impact of such AEs when they occur.

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Compliance with Ethical Standards

Funding This study was made possible by a donation from Dr. Murray Rosenthal. The study funder had no role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

Conflicts of interest Hayley J. Koslik, Athena Hathaway Meskimen, and Beatrice Alexandra Golomb have no conflicts of interest that are directly relevant to the content of this study.

Patient consent Written, informed consent was obtained from each participant for inclusion of their case in this case series.

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